modelling or x-ray crystallography to determine the secondary and tertiary structure and thereby identify the minor groove of the RNA molecule to be inhibited. A compound is designed that will bind to the nucleotides exposed on the surface of the minor groove. The presence of the compound within the minor groove impairs or prevents replication or other functions essential to the survival of the RNA molecule.

The Examiner rejected claims 1-13 under 35 U.S.C. §102(b) as being anticipated by U.S. Patent No. 4,757,055 to Miller *et al.*, U.S. Patent No. 4,898,818 to Nakai, *et al.*, U.S. Patent No. 4,464,359 to Suhadolnik *et al.* (the '359 patent), and U.S. Patent No. 4,924,624 to Suhadolnik *et al.* (the '624 patent).

Miller *et al.* teach a method for inhibiting foreign nucleic acids wherein the base sequence for the foreign nucleic acid is determined and a complementary nonionic oligonucleoside alkyl or arylphosphonate analog is prepared and hybridized to the foreign nucleic acid to prevent replication or expression thereof. Applicant can find no mention of the importance of RNA secondary or tertiary structure in this patent.

Nakai *et al.* teach the preparation and use of the protein "growth inhibiting factor" (GIF) to inhibit tumor growth. Nakai *et al.* use genetic engineering techniques to produce large quantities of GIF and discuss the DNA and amino acid sequences of GIF. Applicant can find no discussion relating to the mechanism of action of GIF in this patent and certainly no mention that GIF binds to any secondary or tertiary structure of RNA.

The '359 patent to Suhadolnik *et al.* discloses an antiviral compound effective against Herpes Simplex Virus (HSV) and Epstein Barr Virus (EBV). The compound is the nucleotide

analog (2'-5')-oligo(3'-deoxyadenylate). The analog apparently produces its anti-viral effect by inhibiting RNA translation, EBV-induced stimulation of DNA synthesis, EBV-induced transformation and HSV Type 1 replication *in vitro*. It appears that the analog activates an endonuclease that then destroys the mRNA of the virus, preventing its replication. This patent fails to disclose direct binding of the analog to any RNA molecule.

The '624 patent to Suhadolnik *et al*. discloses the antiviral activity of 2', 5'-phosphorothioate for treating plant and animal viruses. As in the '359 patent, this antiviral agent activates an endonuclease that destroys the mRNA of the virus and fails to disclose direct binding of the compound to an RNA molecule.

The applicant has amended claim 1 to indicate that the compound binds to the critical site within the minor groove of the targeted RNA. The applicant respectfully submits that none of the cited references, alone or in combination, disclose or even suggest a method where a compound is designed to bind to any tertiary nucleic acid structure and certainly fail to disclose an essential aspect of this method, i.e., that the designed compound bind within the minor groove of the targeted RNA molecule. Therefore, the Examiner's rejection under 35 U.S.C. §102 (b) is respectfully traversed.

The Examiner objected to the specification and rejected claims 1-13 under 35 U.S.C. §112, first paragraph, because specific reaction conditions were not given in the specification. The Examiner noted that incorporation of scientific methods by reference was improper. The Examiner cited several cases for the proposition that essential material should be incorporated

directly into the application by an amendment to the specification. The Examiner's rejection is respectfully traversed.

Section 608.01(p) of the Manual of Patent Examining Procedure defines "essential material" as that which is necessary to (1) support the claims, or (2) for adequate disclosure of the invention. Non-essential material may be incorporated by reference to non-patent publications to indicate the background of the invention or to illustrate the state of the art. All of the methods, reagents and computer software programs described in the references cited in the present application were specifically incorporated by reference as stated on page 39, lines 26-30 of the specification. Other methods and materials used in chemical synthesis and molecular modelling, such as x-ray crystallography, are well known in the art. The applicant respectfully submits that the publications incorporated by reference in the present application are non-essential and merely illustrate the state of the art. Therefore, an amendment to the specification to include the contents of each reference is unnecessary.

The computer programs, such as the CHARMm and QUANTA programs of Polygen Corporation, are described specifically by name, vendor and vendor's location to enable one skilled in the art to obtain a copy of the program and use it to determine the secondary and tertiary structure of the RNA and the portion of the RNA sequence that lies within a minor groove. Incorporation of the entire computer program would be impractical and unnecessary because the programs are commercially available. The applicant respectfully submits that by using the computer program, no methods or reagents are necessary to determine the

secondary and tertiary structure to identify minor grooves once the nucleotide sequence has been determined. DNA and RNA sequencing methods such as the Maxam-Gilbert method and the method of Sanger (also known as the dideoxy method) are well known in the art and are adequately described in current biochemistry texts.

Pursuant to the duty of disclosure under 37 C.F.R. §1.56, the applicant wishes to draw the Examiner's attention to the following publications. These publications have been divided into two categories to facilitate their review. Category I publications relate to RNA molecules in general and Category II publications relate to modelling systems.

Category I publications:

Shi, Jian-Ping, *et al*. Biochem. 29:3621 (1990)

Von der Haar, von Friedrich, *et al*. Angew Chem. 93:250-256 (1981)

Von der Haar, von Friedrich, *et al*. Chem. Abstracts 94:346 No. 197448x (1981)

Brierley, Ian, *et al*. Cell 57:537-547 (1989)

Dreher, T.W. and Hall, T.C. J. Mol. Biol. 201:41-55 (1988)

Jacks, Tyler, *et al*. Cell 55:447-458 (1988)

Pleij, Cornelis, W.A., *et al*. Nucleic Acids Research 13:1717-1731

Haenni, Anne-Lise, *et al*. Progress in Nucleic Acid Research and Molecular Biology 27:85-105

Robertus, J.D., *et al*. Nature 250:546-551 (1974)

Kim, S.H., *et al*. Science 185:435-440 (1974)

Hou, Ya-Ming and Schimmel, P. Nature 333:140-145 (1988)
Park, Soon Jae, *et al*. Biochem. 28:2740-2746 (1989)
Francklyn, Christopher and Schimmel, P. Nature 337:478-481 (1989)
Hou, Ya-Ming and Schimmel, P. Biochem. 28:6800-6804 (1989)
Schimmel, Paul Biochem. 28:2747-2759 (1989)
Hou, Ya-Ming, *et al*. Trends in Biochemical Sciences 14:233-237 (1989)
Schimmel, Paul Cell 58:9-12 (1989)
Endo, Yaeta, *et al*. J. Biol. Chem. 265:2216-2222 (1990)
Park, Soon Jae and Schimmel, P. J. Biol. Chem. 263:16527-16530
Malim, M., *et al*. Cell 60:675-683 (1990)

Category II publications:

Mei, Houng-Yau, *et al*. Proc. Natl. Acad. Sci. 86:9727-9731 (1989)
Roberts, Stanley M., ed. Molecular Recognition: Chemical and Biochemical Problems, CRC Press, 1989
Rebek, Jr., Julius, *et al*. J. Am. Chem. Soc. 107:6736-6738 (1985)
Rebek, Jr., Julius, Science 235:1478-1484 (1987)
Rebek, Jr., J., *et al*. J. Am. Chem. Soc. 109:2426-2431 (1987)
Askew, Ben, *et al*. J. Am. Chem. Soc. 111:1082-1090 (1989)
Williams, *et al*. J. Am. Chem. Soc. 111:1090-1094 (1989)
Benzing, T., *et al*. Science 242:266-268 (1988)

Lewis, R.A., *et al.* Proc. R. Soc. Lond. 236:125-140 (1989)

Lewis, R.A., *et al.* Proc. R. Soc. Lond. 236:141-162 (1989)

Itai, Akiki and Tomioka, N. Chem. Abstracts 108:398 No. 62280y (1988)

Yokoyama, Masayuki, *et al.* Chem. Abstracts 109:79550 No.79541c (1988)

Goodford, Peter Chem. Abstracts 111:126283y (1989)

Badger, John, *et al.* J. Mol. Biol. 207:163-174 (1980)

McKinlay, M. and Rossmann, M. Ann. Rev. Pharmacol. Toxicol. 29:111-122 (1989)

Perry, N.C. and Davies, E.K. in QSAR: Quantitative Structure Activity Relationships in Drug Design, Alan R. Liss, Inc., pp. 189-193 (1989)

Ripka, William, New Scientist 54-56 (June 16, 1988)

Rouvinen, Juba, *et al.* Acta Pharmaceutica Fennica 97:159-166 (1988)

Weber, I., Proteins: Structure, Function, and Genetics 7:172-184 (1990)

Weber, I., *et al.* Science 243:928-931 (1989)

Jones, T.A. and Thirup, S., EMBO Journal 5:819-822 (1986)

As stated above, the following Category I publications relate generally to RNA molecules.

Shi, *et al.* disclose that nucleotides in the acceptor stem of a tRNA molecule affect the efficiency of aminoacylation *in vitro*.

Von der Haar *et al.* disclose studies involving aminoacyl tRNA synthetases. This paper is written in German, and the applicant has not prepared a translation.

Von der Haar, *et al.* (Chem. Abst. 197448x) provides an English abstract of the foregoing publication.

Brierly *et al.* disclose the importance of an RNA tertiary structure termed a "pseudoknot."

Dreher and Hall disclose mutational studies involving the tRNA-like activities of Brome mosaic virus RNA during infection and replication in the plant host.

Jacks, *et al.* disclose the site and mechanism for RNA frameshifting in the Rous sarcoma virus that enable translation of more than one protein from one RNA sequence.

Pleij, *et al.* discuss the formation of pseudoknot structure in RNA molecules. The applicant apologizes for the poor quality of the photocopy and will provide a more legible copy of this paper at the Examiner's request.

Haenni, *et al.* review reports of tRNA-like three-dimentional structures in viral RNA genomes and speculate as to their function.

Robertus, *et al.* and Kim, *et al.* disclose a model of the tertiary structure of yeast phenylalanine tRNA.

The publications of Hou and Schimmel (1988) and Park, *et al.* disclose that a single G-U base pair substitution in the acceptor helix of a tRNA molecule of *E. coli* affects aminoacylation and causes an error in translation.

Francklyn and Schimmel dislose that a synthetic hairpin minihelix composed of only seven base pairs of a $tRNA^{Ala}$ that

confers specificity for aminoacylation of alanine is conserved among insects and humans.

Hou and Schimmel (1989) disclose that a single base pair in the amino acid acceptor stem of an *E. coli* $tRNA^{Ala}$ that confers specificity for aminoacylation of alanine is conserved among insects and humans.

Schimmel (Biochem. 1989) summarizes the basis for recognition of tRNAs by aminoacyl-tRNA syntheses.

Hou, *et al.* review the importance of the G:U base pair of $tRNA^{Ala}$ for aminoacylation by alanine.

Schimmel (Cell, 1989) reviews the interaction of RNA pseudoknots with proteins that regulate mRNA translation.

Endo, *et al.* disclose the interaction of the cytotoxic mold protein alpha-sarcin with a specific site on eukayotic 28 S rRNA which inactivate ribosomes.

Park and Schimmel disclose that bound $tRNA^{Ala}$ synthetase protects several specific sites on the tRNA molecule from ribonuclease attack.

Malim *et al.* disclose that the Rev *trans*-activator of HIV-1 is a sequence-specific RNA binding protein.

As stated above, the following Category II publications relate to modelling systems.

Mei *et al.* disclose use of the program CHARMm to determine the three-dimensional structure of the hammerhead structural domain of the virusoid of lucerne transient streak virus.

The book edited by Roberts contains articles that disclose the use of molecular mechanics interactions to study the energetics of intra-and inter-molecular interactions.

Rebek, *et al.* (1985) disclose the synthesis of a molecular cleft as a receptor for molecules of complementary size, shape, and hydrogen-bonding capacity.

Rebek discloses the development of models for molecular recognition of acids, bases, amino acids, metal ions and neutral substrates and stresses the value of clefts as an active site for molecular interaction.

Rebek *et al.* (1987) disclose the binding of molecules having appropriate size, shape and complementary function to a molecular cleft.

Askew, *et al.* disclose the synthesis and characterization of model receptors for adenine derivatives.

Williams *et al.* disclose the energetics of complexation for model receptors and adenine derivatives.

Benzing *et al.* disclose that synthetic receptors recognize adenine derivatives and transport them across organic liquid membranes and suggest that synthetic receptors be used for drug delivery.

Lewis *et al.* (pp. 125-140) disclose automated site-directed drug design in two dimensions, and specifically discuss the need for "spacer skeletons."

Lewis *et al.* (pp. 141-162) disclose the production of putative ligands from "spacer skeletons" for automated site-directed drug design.

The abstract of Itai and Tomioka reviews computer-aided drug design.

The abstract of Yokoyama *et al.* reviews the molecular design of drugs for targeting cancer cells.

The abstract of Goodford reviews the general principles and problems of drug design with regard to the use of NMR spectrometry.

Badger *et al.* disclose the three-dimensional structures of drug-resistant mutants of human rhinovirus 14 and a comparison to structures predicted by calculations.

McKinlay and Rossmann review the history of anti-viral chemotherapy and suggest that x-ray crystallography and computational chemistry be used to design new anti-viral drugs.

Perry and Davies disclose the use of a three-dimensional modelling database designated "ChemStat" for identifying structure activity relationships for drug design.

Ripka reviews computerized drug development and discloses the combination of molecular biology with computer graphics to create "designer" therapeutic compounds.

Rouvinen *et al.* review computer-aided molecular drug design and discuss the possibility of providing model drug-receptor interactions from the three dimensional structure of a target protein such as a receptor or enzyme.

Weber (1990) compares the crystal structure of chemically synthesized HIV-1 protease to a computer-derived model of the HIV-1 protease based on the crystal structure of a Rous sarcoma virus.

Weber, *et al.* (1989) discloses use of the crystal structure of Rous sarcoma virus to model the three-dimensional structure of an HIV-1 protease.

Jones and Thirup disclose a model for retinol binding protein based on the known three-dimensional structures of three unrelated proteins.

While this statement includes all of the relevant art presently known to the applicant, it should not be construed as a representation that an exhaustive search has been conducted or that no other material information as defined in 37 C.F.R. §1.56(a) exists. Moreover, the applicant invites the Examiner to make an independent evaluation of the cited art to determine its relevance to the subject matter of the present application. Applicant is of the opinion that his claims patentably distinguish over the art referred to herein.

In view of the foregoing remarks and accompanying materials, allowance of claims 1-13 is respectfully solicited.

Respectfully submitted,

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CERTIFICATE OF MAILING (37.C.F.R. 1.8a)

I hereby certify that this paper, along with any paper referred to as being attached or enclosed, is being deposited with the United States Postal Service on the date shown below with sufficient postage as first-class mail in an envelope addressed to the Commissioner of Patents and Trademarks, Washington, D.C. 20231.

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Date: October 16, 1991